REMARKS

Applicants are in receipt of the Examiner's Action dated February 20, 2003, and have the following comments.

The Examiner has responded to the Appeal Brief filed October 15, 2002 by reopening prosecution. Applicants note that the fees already paid by Applicant associated with filing the Notice of Appeal and Appeal Brief will be reapplied to any subsequent filing of such documents by Applicant in an appeal of the Examiner's holdings in this matter.

Rejection of Claims 21-27 under 35 USC 112(1)

The Examiner has alleged that claims 21-27 lack enablement as required by 35 USC 112, first paragraph. Applicants respectfully traverse this rejection.

As the Examiner has stated, the first paragraph of 35 USC 112 requires that the specification describe manner of making and using the invention such that the person of ordinary skill in the art with which the invention is most nearly connected can make and use the same without undue experimentation. The emphasized portion of the previous sentence, exactly as written in the statute, indicates that not only is the disclosure of the specification itself relevant to this analysis, but the knowledge of the person of ordinary skill in such art must also be accounted for when determining whether such a person can make or use the invention described without undue experimentation.

The Examiner has directed the Applicants attention to *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and has cited the so-called *Forman* factors (*Ex parte Forman*, 230 USPQ546 (Bd. Pat. App. & Int. 1986)) in support of the allegation that the recitation in claim 21 of a method of "preventing degeneration of the optic nerve" and "providing protection of the retinal ganglion cells" lacks information that would permit the skilled artisan to determine such prevention or protection without undue experimentation.

It is, of course, a matter of black-letter law that a patent specification need not disclose what is well known in the art. In the present case the article Yavitz, Ocul. Surg. News, 1:17(28) 1999 (which is of record in the prosecution of this application), discusses assay methods for determining that an alpha

2 agonist, brimonidine, "mitigated or totally prevented" nerve fiber thinning caused by raising intraocular pressure. The article explains that raising intraocular pressure is a procedure that "all microkeratomes must do to make a flap" during LASIK eye surgery, and that this procedure "causes nerve loss . . . . due to a crush injury." *Id.* Nerve fiber analysis was performed using a GDx Nerve Fiber Analyzer (Laser Diagnostic Technologies, San Diego) before and after LASIK surgery. *Id.* Thus, methods for determining the prophylactic effect of the claimed combination on nerve cells are clearly well known in the art to which this invention pertains, and a matter of routine.

The Federal Circuit case law used by the Examiner in an attempt to show "undue experimentation", (e.g., *In re Wands*) actually supports Applicants' point of view. In *Wands*, the Court of Appeals for the Federal Circuit reversed the Board of Appeals and Patent Interferences' rejection of claims drawn to an immunoassay method using anti-hepatitis surface antigen (HSA) antibodies. The only issue was whether, in light of only a single deposit of a hybridoma cell line, and in the lack of a single example showing the structure of a high affinity anti-HAS antibody, to obtain such antibodies would require undue experimentation thus rendering the claims non-enabled. In reversing the Board on this point (despite the *Forman* factors) the *Wands* court held that the antibodies could be made using publicly available starting materials and well know methods through "only routine screening". The *Wands* court stated "a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Wands*, 8 USPQ2d at 1404 (emphasis added). Applicants again submit, by these criteria the present invention is completely enabled.

Rejection pursuant to 35 USC Section 102(e)

The Examiner has rejected claims 1, 2, 4, 6, 7, 14, 15, 17, 19, 20-22, 24, and 26-27 under the pre-AIPA 35 USC 102(e), alleging that current 35 USC 102(e) does not apply to the present application because it "was not filed on or after November 29, 2000." Applicants respectfully traverse this rejection.

As stated in the first page of the Examiner's Office Action, the present application was filed July 12, 2001. Thus, this rejection is believed to have been made erroneously applying non-current law.

Rejection pursuant to 35 USC 103(a)

Claims 1-7 and 14-20 were rejected as allegedly unpatentable over Gluchowiski (US Patent 5,091,528) and Bito (US Patent 4,599,353). Applicants respectfully traverse this rejection.

The Examiner contends that Gluchowiski teaches the use of "the claimed alpha 2 agonists" for the treatment of glaucoma, and that Bito teaches the use of "the claimed prostaglandins" for the treatment of glaucoma.

Bito discloses that ocular hypertension and glaucoma can be treated in primates using a topical application of an eicosanoid. Gluchowski discloses certain alpha 2 agonists (of a different generic structure than the structure provided in the claims of the present application) that have ocular hypotensive activity. Neither reference suggests the combination of active ingredients claimed in the present application, nor suggests such a combination that provides the additional benefit of neuroprotection, as is required by the present claims. Thus, considering the present claims as a whole, the combination of these two references does not contain a specific suggestion of or motivation to the presently claimed invention.

The burden is on the Examiner to establish a *prima facie* case of obviousness (rather than on the Applicant to refute the existence of one) and Applicants respectfully contend the Examiner has not done this. Additionally, Applicants hereby incorporate the arguments made against a 35 USC 103(a) rejection in the Appeal Brief filed June 11, 2002 by reference herein. Applicants therein pointed to statements contained in the prior art of record (Searle et al., Drugs and Aging 5:156-170 (1994), indicating that the person of ordinary skill in the art would not have expected that a combination of a prostaglandin and an alpha adrenergic receptor agonist could be used together as a practical therapeutic. For example Searle indicates that the additivity of prostaglandins to other glaucoma medications was at that time "under investigation", even though prostaglandins would "not be expected to be additive" to certain ocular hypotensives *Id.*

Of course, the person of ordinary skill in the art must be deemed to be aware of all the prior art, and the prior art must be considered for all it teaches. See e.g., *In re Dow Chem. Co*, 5 USPQ2d 1529 (Fed.Cir. 1988). Thus, the above-quoted section must be considered by the Examiner, and in

such light in can be clearly seen that the claimed combination is not prima facie obvious in light of the references cited.

Claims 21-27 were rejected as allegedly obvious over Yavitz and Woodward for the reasons set forth in the Office Action of August 19, 2001. The traverse of this rejection was thoroughly made beginning on page 6 of the Appeal Brief filed October 15, 2002; such argument is now incorporated by reference herein. The Examiner states that the Applicants "allege criticality" to the protection of the optic nerve and retinal ganglion cells. However, Applicants in no way alleged criticality of any single element or subset of elements of the claim. The Examiner additionally states that because Applicants spoke to protection of retinal ganglion cells or the optic nerve within the context of glaucoma, a common disease which can exemplify degeneration of retinal ganglion cells and/or the optic nerve, that Applicants arguments are not well taken.

The Examiner is correct that glaucoma is not an element of the claims. But glaucoma is a condition that may commonly involve degeneration of retinal ganglion cells and/or the optic nerve. Thus a discussion of what the prior art has to say about the use of alpha adrenergic agonists and prostaglandins for ophthalmic conditions such as glaucoma that involve neurodegeneration is most certainly relevant to the obviousness of present claims 21-27, since protection of neurons is part of these claims. Moreover, as discussed above with regard to the Searle and in the argument advanced the Appeal Brief, those of skill in the art could have no expectation in light of the prior art that the combination of an alpha adrenergic receptor and a prostaglandin could be formulated together, or would give even additive effects when used together.

For the above reasons, Applicants believe that the present claims are in condition for allowance. Kindly use our Deposit Account No. 01-0885 for payment of any fees, including extension fees, required in connection with this reply.

Respectfully submitted,

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